> transfection does not involve a viral vector. Transfection involves using physical and chemical techniques to introduce a gene into a cell without a viral vector. Indeed, every article the specification cites as teaching transfection methods does not involve using a viral vector to infect cells and deliver a gene. (See specification at 36, lines 7-13).

(Amendment at 14-15). Accordingly, there can be no doubt that Applicant's continuous use of the term "transfection," along with the detailed description of the problems with viral transduction and the absence of the use of any viral vectors or retroviral vectors in the examples, would have conveyed to one skilled in the art that Applicant invented the claimed subject matter.

As further proof that Applicant's specification would have conveyed to one of ordinary skill in the art that Applicant invented a method of transferring a gene into a recipient subject that does not involve a viral vector, a retroviral vector, or DNA of retroviral origin, Applicant submits herewith a copy of the Declaration of Dr. Howard M. Goodman. Dr. Goodman was asked to study the application and indicate if one skilled in the art would have known in 1987 that Applicant invented the claimed subject matter. Dr. Goodman commented:

> 20. In light of the belief of those skilled in the art that methods using retroviral vectors were the best methods for *ex vivo* gene therapy, and their belief that the known problems with retroviral vectors could be overcome, one skilled in the art who read the Selden application in 1987 would have recognized that Dr. Selden invented a composition and a method for transferring a gene into an animal that did not use a retroviral vector or DNA of retroviral origin.
>
> 21. My conclusion that Dr. Selden invented a composition and a method for transferring a gene into an animal that did not use a retroviral vector or DNA of retroviral

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origin would have been further evident from the Selden application's discussion of particular promoters at pages 18-19. One reason many in the field focused upon retroviral vectors was because their own regulatory elements could be used easily. (Ex. 2 at 406, col. 1). The Selden application does not discuss a single retroviral promoter. Rather, the Selden application discusses endogenous promoters from mammals, fruit flies, and yeast. This is striking because retroviral promoters were widely used by those skilled in the art. The absence of any discussion of retroviral promoters, combined with the discussion of the disadvantages and dangers of retroviral vectors and DNA of retroviral origin, would have conveyed to one skilled in the art that Dr. Selden invented a composition and a method of transferring a gene into an animal that does not involve a retroviral vector or DNA of retroviral origin.

22. In addition to discussing problems with using retroviral vectors, in particular, for *ex vivo* gene therapy, the Selden application also discusses problems with using viral vectors, in general, for *ex vivo* gene therapy:

> At present, however, no single technique appears to be wholly satisfactory. The use of viral vectors suffers from their potential for rearrangement of endogenous genes, as well as their potential for inducing carcinogenesis.

(Ex. 4 at 6, lines 27-31).

23. Given the Selden application's discussion of the disadvantages and dangers of viral vector gene delivery systems, especially retroviral vector gene delivery systems, and DNA of retroviral origin, the specification then goes on to describe a solution to these problems, which does not involve the use of viral vectors, retroviral vectors, or DNA of retroviral origin. Specifically, the Selden application describes transfecting somatic cells without a viral vector, without a retroviral vector, and with no DNA of retroviral origin; screening the transfected somatic cells; cloning and expanding a selected somatic cell; and administering the resulting cloned and expanded cells to the recipient subject. (See, e.g., ex. 4 at 12, line 22, through 13, line 6). By not using a viral vector, by not using a retroviral vector, by not using DNA of retroviral origin, by selecting the transfected cells, and by cloning and expanding the selected cells, the Selden application avoids these disadvantages and dangers

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of viral vectors, retroviral vectors, and DNA of retroviral origin.

24. The nonviral aspects of Dr. Selden's invention are further evident from the experiments reported in the Selden application. At a time when workers in field of *ex vivo* gene transfer and gene therapy research had rejected nonviral methods as inherently too inefficient to be useful, and at a time when these workers had turned to the well characterized and easily manipulatable retroviral vectors, none of the experiments the Selden application reports in its 21-pages of examples uses a viral vector, none of the experiments uses a retroviral vector, and none of the experiments uses DNA of retroviral origin.

25. For all these reasons, it is my opinion **the Selden application would have conveyed to one skilled in the art that Dr. Selden invented a composition and a method of transferring a gene into an animal for *ex vivo* gene therapy that did not require the use of a viral vector, a retroviral vector, or DNA of retroviral origin**.

(Goodman Declaration at ¶¶ 20-25; emphasis added).

As Applicant discussed in the Amendment, this is **all** the written description requirement of § 112, first paragraph, requires: That the disclosure convey to one skilled in the art that Applicant invented the claimed subject matter. Vas-Cath, 19 U.S.P.Q.2d at 1117. In other words, the disclosure need only indicate to one skilled in the art that Applicant had possession of the claimed subject matter. Ralston-Purina Co. v. Far-Mar Co., Inc., 227 U.S.P.Q. 177, 179 (Fed. Cir. 1985).

Dr. Goodman's Declaration is further proof that the specification's discussion of the serious problems with viral vectors, retroviral vectors, and DNA of retroviral origin in gene delivery systems; the specification's absence of any other discussion of viral vectors, retroviral vectors, and DNA of retroviral origin; and the specification's use of neither viral vectors, retroviral vectors, nor DNA of retroviral origin in the examples

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would have indicated to one skilled in the art that Applicant had possession of a method of transferring a gene that does not involve a viral vector, a retroviral vector, or DNA of retroviral origin.

Enablement Rejection of Claims 37-71 under 35 U.S.C. § 112, First Paragraph

At pages 24-40 of the Amendment (Section V.), Applicant responded to the Examiner's rejection of claims 37-71 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled by the specification. The Examiner based this rejection on several grounds, including an unsupported assertion that the specification is not enabling for genes or animals other than those used in the examples.

Applicant responded to the rejection on several grounds, including the ground that others have recognized the pioneering nature of Applicant's work (Section V. D.) and the ground that Applicant's early discoveries continue to be used by others outside Dr. Selden's laboratory with different genes and animals (Section V. E.). Applicant discussed and submitted references where others used applicant's method with genes other than the insulin gene and the hGH gene and in animals other than mice. (Amendment at 38-40). For example, the Rosenberg et al. article Applicant discussed at page 38 of the Amendment reported the introduction of the β-nerve growth factor (NGF) gene into rat fibroblasts, which Rosenberg et al. then introduced into rats. (Rosenberg et al., 242 Science 1575 (1988)). Those articles, however, are not the only evidence that others have successfully used Applicant's method with different genes and animals.

Applicant discussed a Rosenthal et al. reference at page 40 of the Amendment. Rosenthal et al. later further acknowledged the contribution of Applicant's method to

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their work. (Rosenthal et al., 20 Onkologie 26 (1997)(copy enclosed)). In a review article, Rosenthal et al. discuss the use of *ex vivo* gene transfer to produce a therapeutic molecule *in vivo*, and they cite Applicant's 1987 *Science* article for this procedure. (Id. at 31, col. 1) The authors then state:

> Ex vivo transfection would allow clonal selection followed by expansion of transfected cells in vitro and a thorough characterization of the cell population reinjected into the patient.

(Id. at 31, col. 2, through 32, col. 1). This is the exact method Applicant discloses in the present application. The authors then discuss their earlier successful work and make it clear that they have consistently used Applicant's method in that work too. (Id.).

Rosenthal et al. continued to build upon their earlier work in 1996, reporting the successful expression of G-CSF in mice injected with G-CSF gene-transfected fibroblasts. (Rosenthal et al., 7 Human Gene Therapy 2147 (1996)(copy enclosed)). The authors again acknowledge Applicant's contribution by citing the Selden 1987 *Science* article and characterizing it as showing that "[g]ene-transfected cells can be used as a source for *in vivo* distribution of a recombinant gene product . . . ." (Id. at 2147, col. 1). Importantly, Rosenthal et al. do not limit this statement to any particular genes or animals.

A 1997 article by Okumura et al. reports the successful use of gene therapy with human Cu, Zn-superoxide dismutase (hSOD) gene-transfected fibroblasts in rats. (Okumura et al., 14 Pharmaceutical Research 1223 (1997) (copy enclosed)). The authors conducted this experiment because "[several studies have shown the feasibility of this approach by transplanting genetically modified fibroblast cell lines into laboratory

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animals and detecting the expression of the heterologous proteins (7, 8)." (Id. at 1223, col. 1). Reference "8" is the Selden 1987 *Science* article.

A 1996 article by Basic et al. reports the successful expression of human growth hormone ("hGH") by implanting hGH gene-transfected fibroblasts into mice. (Basic et al., 24 Artificial Cells, Blood Substitutes, and Immobilization Biotechnology 219 (1996) (copy enclosed)). Basic et al. obtained similar results to the results in the present application and specifically discuss the Selden 1987 *Science* article five different times. (Id. at 220, 244-49, 251-3). Like the present application, Basic et al. believed the eventual decline in hGH production resulted from the host's immune system attacking the allogeneic transfected cells. (Id. at 248). Basic et al. conclude that "the novel gene product, hGH, is delivered *in vivo*." (Id. at 252).

Finally, and perhaps more importantly, Applicant's methods have become so accepted by those who are familiar with them that they are now being used as reliable tools to study other physiological processes. In other words, Applicant's methods have become so accepted that their use is no longer considered to be a variable. Rage et al. postulated that inappropriate activation of transforming growth factor α ("TGFα") expression near luteinizing hormone-releasing hormone ("LHRH") can induce female sexual precocity. (Rage et al., 94 Proc. Natl. Acad. Sci. USA 2735 (1997) (copy enclosed)). "To test this assumption, [Rage et al.] used the somatic cell gene therapy approach of transkaryotic implantation (10) for targeting TGFα over expression near LHRH neurons [in rats]." (Id. at 2735, col. 2). Reference "10" is a citation to Applicant's 1987 *Science* article.

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These articles show that Applicant enabled those skilled in the art to use his method to successfully transfer various genes into various animals, not just the insulin and hGH genes into mice. In addition to the articles Applicant submitted with the Amendment of March 11, 1998, these articles show that Applicant's enabling teachings are so strong that Applicant's method has been consistently used for over ten years, and it has been used with different promoters, different genes, different cells, and different animals than Applicant used.

Furthermore, it must be remembered that these articles cite the 1987 Selden et al. *Science* and *New England Journal of Medicine* articles, which, together, only contain some of the enabling teachings and data contained in the present application. In other words, the present application contains more information than the 1987 Selden et al. *Science* and *New England Journal of Medicine* articles, and these articles enabled others to use Applicant's invention with different genes and animals than Applicant used. Given this evidence, there can be little doubt that the present application would have enabled one skilled in the art to use the claimed method with genes other than the hGH and insulin genes and with animals other than mice, and Applicant respectfully requests that the Examiner allow the pending claims so that the additional information contained in this application will be published now, over ten years later.

Conclusion

Applicant surprisingly showed that *ex vivo* gene transfer could be accomplished with nonviral transfection. Applicant's showing was so strong that it enabled those who were aware of Applicant's work to successfully practice *ex vivo* gene transfer without using viral or retroviral vectors. It has even enabled numerous researchers to practice

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ex vivo nonviral gene transfer with numerous promoters, genes, cells, and animals. Indeed, Applicant's teachings are so strong that they have enabled TKT to receive FDA approval for ongoing clinical trials in humans.

In view of the extensive evidence of the nonobviousness and the enablement of the claimed invention in the Amendment and this Supplemental Response, Applicant respectfully submits that the claims are in condition for allowance. Applicant respectfully requests that the Examiner acknowledge what the authors of the numerous articles have acknowledged—that Applicant's teachings are novel, nonobvious, and enabling—and allow the pending claims so that Applicant's pioneering work will be published in the U.S. in the form of a U.S. patent.

Request for Interview

If the Examiner does not believe that each and every claim is in condition for allowance, Applicant respectfully requests the Examiner to contact the undersigned to schedule an interview with the Examiner and his Supervisory Patent Examiner before the Examiner acts upon the Amendment and this Supplemental Response.

Respectfully submitted,

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Date: June 24, 1998

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